REMARKS

The specification has been amended as set forth above. The amendment to the paragraph beginning at line 26 of page 8 is supported by the specification as filed. Specifically, U.S. Patent No. 5, 459,127 (the '127 patent) was incorporated by reference in its entirety, and all of the amended material has been taken *verbatim* from the '127 patent. Thus, no new matter has been added.

Upon entry of the claim amendments, set forth above, Claims 1-3, 5-12, 14-25, 27-41 and 43-46 are pending in the present application. Claims 1, 10, 21, 38 and 44 have been amended. Accordingly, Applicants respectfully submit that the application is now in condition for allowance.

The amendments to the specification and to the claims are shown by ~~strikethrough~~ for deleted matter and underlining for added matter.

Support for the amendments can be found throughout the specification and in the claims as originally. Accordingly, no new matter has been added to the application by entering this amendment.

Discussion of Specification Objections Under 35 U.S.C. § 132

The Examiner objected to the amendment to the specification filed on January 22, 2002 arguing that it introduced new matter into the disclosure. As set forth above, the objected to paragraph in the specification has been amended, thereby mooting the objection.

Discussion of Rejection Under 35 U.S.C. § 112, first paragraph

The Examiner rejected Claims 9, 19, 25, 37 and 45 as allegedly failing to comply with the written description requirement. According to the Office Action, the claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

To satisfy the written description requirement, a patent application must describe the invention in sufficient detail that one of skill in the relevant art could conclude that the inventor

was in possession of the claimed invention at the time the application was filed. *See Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, (Fed. Cir. 1991).

Applicants respectfully assert that Claims 9, 19, 25, 37 and 45 are supported by the application as filed, and specifically in view of the amendment to the specification. As amended the specification recites what was previously incorporated by reference; *i.e.*, the use and delivery of phosphorothioated nucleic acids, thereby showing possession of the claimed subject matter. Therefore, Applicants request reconsideration and withdrawal of the instant written description rejection.

Discussion of Rejections Under 35 U.S.C. § 102

Claims 10, 11, 14 and 16 were rejected under 35 U.S.C. § 102(a) as being anticipated by Cassata et al., (referred to hereafter as "Cassata") "Rapid expression screening of *Caenorhabditis elegans* homeobox open reading frames using a two-step polymerase chain reaction promoter-gfp reporter construction technique," *Gene*, Vol. 212, pages 127-135, 1998. Claims 1, 2, 5, 6, 10, 12, 14, 15, 21, 22, 27-29, 30-34 and 46 were rejected under 35 U.S.C. § 102(b) as being anticipated by Prodromou et al., (referred to hereafter as "Prodromou") "Recursive PCR: a novel technique for total gene synthesis," *Protein Engineering*, Vol. 5, pages 827-829, 1992.

To be anticipatory under 35 U.S.C. § 102, a reference must teach each and every element of the claimed invention. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379 (Fed. Cir. 1986). "Invalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference. ...There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention." *See Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565 (Fed. Cir. 1991).

Respectfully, for the reasons set forth below, the rejected claims are not anticipated by the cited references, because neither reference teaches each and every element of the claims.

Cassata

Cassata fails to teach each and every element of amended independent Claim 10 and dependent Claims 11, 14 and 16.

Independent Claim 10 has been amended as set forth above to recite, *inter alia*, "contacting a second primer pair with the second nucleic acid fragment and with a third nucleic acid fragment that comprises a region complementary to the extension region and also a nucleic acid sequence that confers function." As discussed during the January 28, 2004 interview, Cassata does not teach PCR amplification with a "second primer pair." Therefore, Claim 10 and Claims 11, 14 and 16 are not anticipated by Cassata, because Cassata fails to teach each and every element of independent Claim 10 as amended.

Prodromou

Prodromou fails to teach each and every element of independent Claims 1, 10, and 21 because Prodromou fails to disclose methods that include, *inter alia*, more than one or sequential PCR steps. Prodromou is significantly different from the claimed methods and systems. Prodromou sought to assemble synthesized nucleic acid fragments in order to construct a longer gene. *See* page 827, paragraph 1. Prodromou discloses a single PCR reaction mix that includes 10 synthetic fragments. Prodromou attempted to use a single step PCR mix to assemble a 522 base pair human lysozyme gene. As discussed during the January 28, 2004 interview, Prodromou does not teach sequential addition of functional segments. Therefore, Prodromou does not anticipate independent Claims 1, 10 and 21.

Also, Prodromou fails to teach each and every element of Claim 30. Amended Claim 30 recites a system for adding a nucleic acid fragment that confers function to a polynucleotide target sequence. The system includes an extension primer pair comprising a 5' and a 3' primer, wherein the 5' primer comprises a region of complementarity to a 5' strand of the polynucleotide target sequence and a predetermined extension region, and wherein the 3' primer comprises a region of complementarity to a 3' strand of the polynucleotide target sequence and a predetermined extension region. The system also includes a 5' biological function conferring nucleic acid fragment and a 3' biological function conferring nucleic acid fragment, each fragment of which comprises a region of complementarity to one of the extension regions, and a biological function conferring polynucleotide sequence that confers biological function.

Prodromou does not disclose such a system with the same elements. Furthermore, the elements disclosed by Prodromou do not have the same relationship to each other as those in

Claim 30. For example, Prodromou fails to disclose an extension primer pair as set forth in Claim 30. Also, Prodromou fails to disclose a 5' biological function conferring nucleic acid fragment and a 3' biological function conferring nucleic acid fragment, each with a region complementary to one of the extension regions on the extension primer pair. Prodromou did not disclose such primers and biologic function conferring nucleic acid fragments with complementary regions for a particular fragment. To the extent Prodromou disclosed any type of functional fragment, it did not have complementary sequence for the same target fragment.

Prodromou simply sought to assemble multiple synthetic DNA fragments using PCR enzymes. *See* page 827, paragraph 1. Also, these synthetic fragments assembled together by PCR are not a target sequence as recited in rejected independent Claim 30. Thus, Prodromou does not anticipate Claim 30.

For the reasons set forth above, Prodromou does not anticipate amended independent Claims 1, 10, 21 and 30, or the claims depending therefrom, because it fails to teach each and every element of the claims. Therefore, reconsideration and withdrawal of the § 102 rejections is respectfully requested.

Discussion of Rejection Under 35 U.S.C. § 103(a)

The Examiner rejected Claims 3, 7-9, 17-20, 23-25, 35-45 under 35 U.S.C. § 103(a) as being unpatentable over Prodromou combined with various other references. Specifically, the Office Action rejects Claims 3, 20, 23 and 35 over Prodromou in view of Felgner et al. (referred to hereafter as "Felgner"), U.S. Patent No. 6,165,720. Claims 7, 8, 17, 18, 24, 25, 36 and 37 were rejected over Prodromou in view of Uhlman et al. (referred to hereafter as "Uhlman"), U.S. Patent No. 6,063,571. Also, Claims 7, 9, 17 and 19 were rejected over Prodromou in view of Goodchild, "Conjugates of Oligonucleotides and Modified Oligonucleotides: A Review of Their Synthesis and Properties," *Bioconjugate Chemistry*, Vol. 1, pages 165-187, 1990. Furthermore, Claims 38-43 were rejected over Prodromou and Mullis et al. (referred to hereafter as "Mullis"), U.S. Patent No. 4,965,188. Finally, Claims 44 and 45 were rejected over Prodromou and Uhlman.

To establish a *prima facie* case of obviousness a three-prong test must be met. First, there must be some suggestion or motivation, either in the references or in the knowledge generally

available among those of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success found in the prior art. Third, the prior art reference must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

The motivation to combine references must come from the references themselves and not from the invention. *See In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988). The case law "makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine the prior art references." *Echolochem, Inc. v Southern California Edison Co.*, 227 F.3d 1361, 1371 (Fed Cir. 2000) (quoting *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999)).

Respectfully, none of the cited combinations teach or suggest all of the claim limitations, nor is there any motivation to combine absent impermissible hindsight. Therefore, none of the claims are obvious over the cited combinations of references.

Prodromou and Felgner

As mentioned above, the Office Action rejected Claims 3, 20, 23 and 35 over Prodromou in view of Felgner. Claims 3 and 20 depend from independent Claim 1, Claim 23 from independent Claim 21, and Claim 35 from independent Claim 30. Prodromou does not teach each and every element of those independent claims for the reasons set forth above. Specifically, for example, Prodromou does not disclose methods that comprise sequential target sequence amplification. Instead, Prodromou assembled synthetic nucleic acid fragments using a single PCR step. Also, Prodromou fails to disclose the elements of system Claim 30, for the reasons discussed above.

Felgner disclosed chemical modification of DNA using peptide nucleic acids (PNAs). Thus, Felgner also does not disclose methods comprising sequential amplification of target nucleic acids. Felgner also does not disclose the elements of system Claim 30. Therefore, the combination of Prodromou and Felgner fail to teach or suggest all of the claim elements.

Prodromou and Uhlman

Claims 7-8, 17-18, 24-25 and 36-37 were rejected over Prodromou and Uhlman. All of the claims respectively depend from independent claims 1, 21, or 30. As discussed above, Prodromou does not teach each and every element of those independent claims, specifically for example, Prodromou fails to disclose methods that comprise sequential target sequence amplification, and fails to disclose the elements of system Claim 30. Uhlman disclosed a process for amplifying nucleic acids using DNA/PNA primers. Thus, Uhlman also does not disclose methods comprising sequential amplification of target nucleic acids, or systems with the elements of Claim 30. Therefore, the combination of Prodromou and Uhlman fail to teach or suggest all of the claim elements.

Also, Claims 44 and 45 were rejected over Prodromou and Uhlman. Claim 44 recites methods comprising sequential PCR amplification of, *inter alia*, a polynucleotide target sequence. For reasons similar to those discussed above, neither Prodromou or Uhlman, alone or combined teach or suggest such methods.

Prodromou and Goodchild

Claims 7, 9, 17 and 19, all of which depend from amended Claim 1, were rejected over Prodromou and Goodchild. Prodromou does not disclose each and every element of Claim 1, including for example, sequential amplification of a target fragment of DNA, as already discussed above. Goodchild discloses a review of the synthesis and properties of conjugates of oligonucleotides and modified oligonucleotides. Therefore, Goodchild also does not teach or suggest, for example, methods comprising sequential PCR amplification of a target fragment of DNA.

No Suggestion or Motivation to Combine the Prodromou with the Felgner, Uhlman or Goodchild

Furthermore, only with hindsight motivation based upon the claims are the combinations of Prodromou with each of Felgner, Uhlman or Goodchild made. Prodromou recognized the difficulty in the early 1990s of synthesizing genes, even small genes, and provided a methodology for overcoming that difficulty. Prodromou was not concerned with nuclease resistance, but simply sought to validate the possibility of assembling synthetic fragments to

construct larger sequences. Felgner, Uhlman and Goodchild all relate to PNA technology. Thus, the references are directed to different objectives and provided no suggestion or motivation to combine absent hindsight.

Prodromou in view of Mullis

The Office Action rejects Claims 38-43 as being unpatentable over Prodromou and Mullis. Neither Prodromou or Mullis, alone or combined, discloses a method for creating transcriptionally-active nucleic acid sequences from a plurality of different target polypeptide-encoding DNA sequences. Also, neither Prodromou or Mullis, alone or combined, discloses sequential PCR amplification steps as set forth in Claim 38. As discussed above, Prodromou does not disclose methods comprising sequential PCR amplifying of target sequences. Prodromou discloses the assembly by PCR of a synthetic nucleic acid sequence. Mullis discloses general PCR methods, and thus has nothing to add to the recursive PCR methodology of Prodromou. Mullis does not disclose the claimed method comprising a plurality of target polypeptide-encoding DNA sequences. Therefore, the references alone or combined do not teach or suggest all of the limitation of independent Claim 38 and the claims depending therefrom.

Furthermore, there is no suggestion or motivation to combine the references absent illicit hindsight reconstruction. Prodromou assembled synthetic oligonucleotides using PCR, and thus disclosed no target polypeptide. It is illogical to combine such a reference with Mullis, a patent covering the general concept of PCR, to achieve the claimed method, absent hindsight. For these reasons no motivation to combine exists in the references.

For all of the above reasons, Applicants respectfully request withdrawal of all rejections under 35 U.S.C. § 103, and allowance of the pending application.

CONCLUSION

For the foregoing reasons, it is respectfully submitted that the rejections set forth in the outstanding Office Action have been addressed and that the application is now in condition for allowance. Accordingly, Applicants request the expeditious allowance of the pending claims.

The undersigned has made a good faith effort to respond to all of the rejections in the case and to place the claims in condition for immediate allowance. Nevertheless, if any undeveloped issues remain or if any issues require clarification, the Examiner is respectfully requested to call the undersigned to discuss such issues.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 3/19/04

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